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10/552,369	10/07/2005	Rikiichi Tagawa	TAGAWA1	1884

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EXAMINER	
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ART UNIT	PAPER NUMBER
1654	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/552,369	TAGAWA ET AL.	
	Examiner	Art Unit	
	MARCELA M. CORDERO GARCIA	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 December 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 2-9 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 2-9 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is in response to the reply received on 11 December 2008.

Claims 2-9 are pending in the application. Claims 2-5 have been amended by Applicant. Claims 8-9 are new claims.

Any rejection from the previous office action, which is not restated here, is withdrawn.

Claims 2-9 are presented for examination on the merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2-5 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants have introduced the limitation in claim 2 as underlined; "before a heat treatment sufficient to inactivate virus in a liquid state".

New Matter

The claims have been amended (cf. amendment filed 11 December 2008) to limit the heat treatment to heat treatment sufficient to inactivate virus. Applicants did not expressly state that the amendments add no new matter, nor have the portions of the application supporting such amendment been pointed out.

Lack of Ipsis Verbis Support

The specification is void of any support that would clearly support the instant amendment. The specification does not teach the newly recited "sufficient to inactivate virus" limitation. Therefore it is deemed that the disclosure does not provide literal support for the amendment adding the term "heat treatment sufficient to inactivate virus in a liquid state".

Lack of Inherent Support

"While there is no in haec verba requirement, newly added claim limitations must be supported in the specification through express, implicit, or inherent disclosure." See MPEP 2163. Based on the disclosure page 16 teaches the use of heat treatment, but it is silent as to virus inactivation. Page 3 does teach that after 60 C for 10 hrs, the solution needs to be filtrated "as a measure for inactivation/removal of pathogens such as viruses not being inactivated/removed through the above processes or unknown pathogens such as viruses that have not yet been found". Moreover, in pages 2-3, applicant teaches in the last paragraph that "For inactivation of viruses, a possibility of whose contamination in a preparation from blood, i.e., a blood preparation, is not denied, heat treatment has commonly been used." However, in page 3, Applicant goes on to say that "[a]ll this approaches have both merits and demerits and each of individual approach alone would not likely provide complete removal of viruses.". Therefore, the heat treatment 'sufficient to inactivate virus' limitation is deemed to be new matter, as the disclosure does not expressly or inherently provide guidance for such limitation.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2, 4, 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Winge (US 6,399,357) in view of Chang (US 5,250,662).

Winge teaches a process for preparing an albumin preparation for therapeutic use (column 1, lines 35-67; column 2, lines1-10) which involves a step of filtration with a virus-removing membrane (e.g., claims 49, 54-56), e.g., with a pore size of 10-20 nm as in Viresolve 180 (e.g., column 5, lines 40-65).

Winge does not teach doing a heat treatment sufficient to inactivate virus in liquid state after the filtration with a virus-removing membrane or use of an anion exchanger before the filtration with a virus-removing membrane.

Chang teaches a purification method of albumin comprising heat-shocking the stabilized albumin solution for 2 hours at 60º C (e.g., column 18, lines 42-45) as in the limitation of claim 2: "heat treatment sufficient to inactivate virus in a liquid state". Please note that the limitation is not drawn to any specific amounts of virus inactivation and that heating a sample for 2 hrs at 60 C does necessarily read upon virus inactivation, since the claim is not drawn to a specific amount of inactivation. Additionally, Chan et al. teach ultrafiltration with Millipore 10 K NMWL (col. 7, lines 50-55 and col. 18, lines 53-62). Chan et al. teach that albumin's main uses are as a plasma extender and for

correction of hypoproteinemia. In addition, albumin is frequently used: (1) as stabilizing agent for other proteins contained in preparations administered for various treatments such as Factor VIII; (2) to maintain the colloid osmotic pressure; and (3) for in vivo transport functions, for example, of fatty acids and drugs (column 1, lines 38-44). Chan et al. also teach use of anion-exchange resin (as in the limitation of claims 4 and 6: "anion exchanger") to remove contaminants from an albumin-containing preparation (e.g., claim 1) for therapeutic uses (e.g., column 1, lines 38-44).

Neither reference expressly teaches the order of purification steps as instantly claimed.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Winge by using a combination of purification steps including heat treatment or anion exchange filtration (column 18, lines 42-45; claim 1) as taught by Chang. The skilled artisan would have been motivated to do so in order to further purify the albumin. There would have been a reasonable expectation of success, given that both Winge and Chan et al. teach purification of albumin for therapeutic applications (column 1, lines 35-67; column 2, lines1-10 of Winge; column 1, lines 38-44 of Chang). The adjustment of particular conventional working conditions (e.g., determining appropriate purification steps and order of the steps within such method) is deemed merely a matter of judicious selection and routine optimization that is well within the purview of the skilled artisan. As such, it would have been obvious to one skilled in the art at the time of invention to determine all optimum and operable conditions (e.g., determining types of purification steps including anionic

exchange filtration, heat treatment and virus-filtration, and order thereof), because such conditions are art-recognized result-effective variables that are routinely determined and optimized in the art through routine experimentation ("[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.". *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). See MPEP 2145.05). One would have been motivated to determine all optimum and operable conditions in order to achieve the highest yield of the highest purity product in the most efficient manner. One would have had a reasonable expectation for success because such modifications are routinely determined and optimized in the art through routine experimentation.

From the teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Claims 2 and 3, 5, 7- 9 are rejected under 35 U.S.C. 103(a) as being unpatentable Winge (US 6,399,357) in view of Chang (US 5,250,662), http://www.asahi-kasei.co.jp/planova/en/product/filters.html (accessed online 6/4/08) and Burnouf (Virol. Safety Aspects of Plasma Derivatives, 1993, cited in the IDS of 01/06).

Winge and Chang are relied upon as above. Winge also teaches that the degree of fineness of the filters is normally given as pore size or the approximate molecular weight at which the molecules are stopped by the filter. Winge goes on to teach Planova

filters Planova 15 and Planova 35 which are used for smaller viruses (column 5, lines 50-54).

http://www.asahi-kasei.co.jp/planova/en/product/filters.html teaches that Planova filters are available in single-use, self-contained modules in mean pore sizes of 15 nm and 35 nm as in the instant limitations of claims 3, 5 and 7 [column 5, lines 50-54]. Winge teaches that the method reduces the residence time and the extent to which the solution needs to be diluted and optimizes the yield when virus-filtering primarily proteins (e.g., column 1, lines 15-23).

Burnouf et al. teach viruses of various sizes and shapes [pages 201-203], including the smallest parvoviridae virus being 18-26 nm in diameter (as in instant claim 3: "pore size 10-20 nm") and the largest poxviridae 300-45 x 170x260 nm in size (as in instant claims 5, 7 and 9: "pore size 35-200 nm) in plasma derivatives.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods of Winge and Chang by expressly selecting a pore size of 10-20 nm (see column 5, lines 40-64of Winge) or prefilter at a pore size of 35-200 nm (e.g., Winge, column 5, lines 40-64). The skilled artisan would have been motivated to do so in order to purify the albumin with a smaller time of residence and optimized yield as taught by Winge (column 1, lines 15-23) for purification from viruses such asparvoviridae which is 18-26 nm in diameter (Burnouf, pages 201-203; Winge, column 5, lines 50-54). There would have been a reasonable expectation of success, because Winge teaches 15 nm pore size filters Planova 15 and 35 nm Planova 35 (http://www.asahi-kasei.co.jp/planova/en/product/filters.html) and because filtration of

larger viruses such as poxviridae (300-45 x 170x260 nm in size) was also known in the art (Burnouf, pages 201-203, Winge column 5, lines 50-54) and because Winge, Chang, and Burnouf teach purification of albumin/plasma derivatives for therapeutic applications. The adjustment of particular conventional working conditions (e.g., determining appropriate purification steps including prefiltration from within those taught by the prior art, determining appropriate order of the steps and/or selecting appropriate size pores for filtration within such method) is deemed merely a matter of judicious selection and routine optimization that is well within the purview of the skilled artisan. As such, it would have been obvious to one skilled in the art at the time of invention to determine all optimum and operable conditions (e.g., filtration pore size, purification steps, and order thereof), because such conditions are art-recognized result-effective variables that are routinely determined and optimized in the art through routine experimentation ("[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.". *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). See MPEP 2145.05). One would have been motivated to determine all optimum and operable conditions in order to achieve the highest yield of the highest purity product in the most efficient manner. One would have had a reasonable expectation for success because such modifications are routinely determined and optimized in the art through routine experimentation.

From the teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed

invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments

Applicants submit that a modification of Winge would not have been obvious, and that even if it were obvious to modify Chang in view of Winge, the resultant reconstructed Winge would not correspond with the claimed subject matter.

Chang broadly discloses a method of purifying albumin using a combination of precipitation and anion-exchange chromatography. The rejection focuses on Chang at col. 8, lines 42-43, part of example 9, which states as follows:

> Heat-shocking of the stabilized albumin solution was then performed for two hours at 60 C, using a circulating glycerol heating system. After the two-hour heat-shock, the solution was chilled to 9 C.

Applicants respectfully submit that there is no reason one would have adopted the heat-shocking procedure of Chang's example 9 for incorporation into and modification of Winge for reasons pointed out below; and that even if such a heat-shocking operation were incorporated into Winge, it would not result in applicant's embodiments as called for in claim 2. In this regard please consider the following facts:

First, example 9 of Chang relates to a purification method (acetone and heat-shock purification) which was prior to Chang, and compares the prior art example 9 process with the process of Chang. Chang thus teaches away from the prior acetone

and heat-shock purification method. It cannot be considered to have been obvious to adopt something from Chang which Chang effectively denigrates.

Second, the heat-shock treatment of example 9 of Chang is not intended to inactivate virus. There is no indication in example 9 of Chang of the presence of any virus, and there is no certainty that the heat-shocking performed for two hours at 60 C would inactivate virus if any virus were present.

Third, although Chang mentions several filtration steps in the criticized example 9 processes, the filtration is not related to the removal of virus. Again, no virus is disclosed as being present. Applicants respectfully ask what reason would the person of ordinary skill in the art have for adopting the heat-shocking and filtration steps of Chang for removing virus when example 9 of Chang does not even indicate the presence of virus. Respectfully, there is no reason.

Fourth, the filtration of example 9 of Chang with the 90 S filter (col. 18, lines 46-49) was carried out after the heat-shocking treatment, which is just the reverse of the process of the present invention, where the filtration is carried out before the heat treatment. In this regard, again, Chang teaches away from the present invention. Adopting such a filtration with the 90 S filter would be contrary to the embodiments of claims 2 and 4.

With regards to claim 6, it covers embodiments wherein the albumin-containing solution is first subject to anion-exchange and/or a prefilter and then to filtration with a virus-removing membrane.

Winge discloses virus filtering, but not the preliminary steps of claim 6. Chang, at col. 1 lines 38-44, simply discloses uses for albumin, regarding which there is no dispute. Otherwise, the rejection appears again to rely only on the denigrated process of Chang's example 9, which has nothing to do with freeing albumin of virus. Applicants see no reason given in either Winge or Chang to employ an earlier prefiltration and/or anion-exchange prior to filtration with virus-removing membrane of Winge. The combination only appears in retrospect to have been obvious, but it was not obvious at the time the present invention was made.

With respect to the commentary appearing at the bottom of page 4 and carrying over to the top of page 5, applicants respectfully submit that reliance on In re Aller is unjustified, because the Court in Aller acknowledged that conditions and parameters cannot be brushed aside if they produce a different result. It will be seen from example 1 of the present application (pages 16 and 17), that the results produced according to the present invention are substantially improved as shown in Figure 1 (see page 17, lines 7-14).

Claims 1, 3, 5, and 7 have been rejected under Section 103 as obvious from Winge in view of Chang as applied against claims 2 and 6, and further in view of Burnouf, citation AH, and a reference entitled: Planova Filters.

First, claims 3 and 5 depend from and incorporate the features of claim 2. Burnouf and Planova have not been cited to make up for the deficiencies of the proposed combination of Winge in view of Chang as pointed out above, and do not do so.

Therefore, even if further modification of Winge in view of Burnouf and Planova were obvious, the so modified Winge would not reach even claim 2, let alone claims 3 and 4. the same applies to claim 7 which depends from and incorporaties the features of claim 6.

Applicants respectfully note that they have never alleged to be the inventors of the filters in question, or to have discovered the size of the viruses eliminated according to the present invention. Instead, the present invention relates to a process which accomplishes a particular objective in a new and non-obvious way, and which results in the unexpected improvements which are pointed out in applicant's specification, including example 1.

Response to Arguments

Applicant's arguments filed 11 December 2008 have been fully considered but are not deemed persuasive for the reasons of record and for the following reasons:

With regards to the statement that "the heat-shock treatment of example 9 of Chang is not intended to inactivate virus" this statement is not substantiated by the Applicant. The Chang reference teaches purification of albumin from contaminants in general. The conditions of 60 C are also taught by the Applicant as virus-inactivating (see page 16). There has not been any evidence presented as to heat application at 60 C for 2 hrs would not cause virus inactivation.

Additionally, with regards to the statement that "there is no reason" to combine Winge and Chang, it is respectfully noted that both Winge and Chang teach purification

of albumin and that combining purification steps in order to further purify a composition is well within the purview of one skilled in the art and sufficient motivation to proceed.

Applicant states that using a 90 S filter as in Chang would teach away from the instant invention, however, please note that the instant process does not exclude other steps from being carried on. Additionally, please note Chang does teach ultrafiltration, e.g., with a Millipore Pellicon cassette 10K NMWL (col. 7, lines 50-55 and col. 18, lines 50-65). Additionally, with regards to the order of steps and the statement that the results produced according to the present invention are substantially improved as shown in Figure 1 (see page 17, lines 7-14), it is noted that Figure 1 shows filtration properties in filtration processes using a virus-removing membrane as incorporated into a process for preparing an albumin preparation in accordance with the present invention. It does appear that the volume of filtrate (L/m2) is greatest before heat treatment and less after the heat treatment however, the disclosure is not clear as to whether this volume also reflects a greater amount of albumin getting through. In other words, it is not clear what the concentration of albumin is in each filtrate of Figure 1.

With regards to the arguments regarding *In re Aller*, it is noted that, despite the fact that a motivation for combining the references has been provided above, it has been held that under KSR that "obvious to try" may be an appropriate test under 103 The Supreme Court stated in KSR:

> When there is motivation "to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to

try might show that it was obvious under § 103." KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727, ___, 82 USPQ2d 1385, 1397 (2007).

The "problem" facing those in the art was the purification of albumin, and there were a limited number of methodologies available to do so. The skilled artisan would have had reason to try these methodologies with the reasonable expectation that at least one would be successful. In the instant case the three methods: heat treatment, filtration at 10-20 nm or 35-200 nm and anion-exchanger were taught by the prior art as useful for purifying albumin as set forth above. Thus, purifying albumin is a "the product not of innovation but of ordinary skill and common sense," leading to the conclusion that invention is not patentable as it would have been obvious.

In addition, KSR forecloses the argument that a specific teaching, suggestion or motivation is required to support a finding of obviousness.

See the recent Board decision Ex parte Smith, --USPQ2d--, slip op. at 20, (Bd. Patt. App. & Interf. June 25, 2007) (citing KSR, 82 USPQ2s at 1396) (available at http://www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf).

Conclusion

No claim is allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARCELA M. CORDERO GARCIA whose telephone number is (571)272-2939. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia J. Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Anish Gupta/
Primary Examiner, Art Unit 1654

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Examiner, Art Unit 1654

MMCG 02/09